# Case Reports

## The Corticotropin-Releasing Factor Test in the Diagnosis of Ectopic ACTH Secretion

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THE DIFFERENTIAL DIAGNOSIS between pituitary Cushing's syndrome (Cushing's disease) and ectopic adrenocorticotropic hormone (ACTH) secretion can be deceptive because the sensitivity and specificity of the traditional pharmacologic tests are not optimal. Recently the corticotropin-releasing factor (CRF) stimulation test has been proposed as a helpful tool in the differential diagnosis of Cushing's syndrome. We report a case that underlines the usefulness of this new test.

### Report of a Case

A 73-year-old woman was admitted to a local hospital in September 1984 with weakness, central obesity, type II diabetes mellitus of new onset, increase in facial hair and easy bruising. Her history was remarkable for resection of a Dukes' B2 adenocarcinoma of the colon in September 1980, new-onset sixth cranial nerve palsy in October 1983 and abnormal liver function since February 1984. She had been taking chlorpropamide, furosemide and potassium chloride. On physical examination she showed occasional disorientation, multiple ecchymoses, hirsutism and central obesity. The liver was enlarged but nontender; there was left sixth cranial nerve palsy and severe bilateral proximal lower extremity weakness. Laboratory values included normal electrolytes; aspartate aminotransferase (formerly SGOT) 66, alanine aminotransferase (formerly SGPT) 72, lactic dehydrogenase 736 and alkaline phosphatase 332 IU per liter; total bilirubin 1.5 mg per dl. Plasma cortisol levels were elevated (28 and 30 μg per dl in the afternoon), as were the plasma ACTH levels (118 and 139 pg per ml), and the urinary 17-hydroxycorticoids failed to suppress with the administration of both 2 mg of dexamethasone (from a base line of 12.0 to 13.2 mg per 24 hours) and 8 mg of dexamethasone (12.9 mg per 24 hours). These data were interpreted as suggestive of ectopic ACTH secretion. Further studies included chest and abdominal computed tomographic (CT) scans that showed bilateral adrenal enlargement, two lucencies in the liver (unchanged since 1981) and a questionable thickness in the tail of the pancreas. CT-scan-guided pancreatic biopsy yielded only a few normal pancreatic cells.

At this juncture the possibility of a pituitary source of ACTH was reconsidered. A "very high" dexamethasone test (32 mg) showed suppression of the 17-hydroxycorticoids (from a base line of 12.0 to 5.8 mg per 24 hours), and a metyrapone test showed appropriate increase of plasma 11-deoxycortisol to 24 μg per ml. These results were interpreted as being consistent with pituitary Cushing's syndrome, and the patient was transferred to the University of California, San Diego, Medical Center on October 28, 1984. A CRF stimulation test (1 μg per kg body weight) showed no increase in plasma cortisol levels (35 μg per dl at base line and 32 to 36 μg per dl up to 120 minutes after CRF was given) and bilateral inferior petrosal sinus catheterization showed no gradient in ACTH levels (106 pg per ml in the right sinus, 150 pg per ml in the left sinus and 133 pg per ml in the inferior vena cava). A liver biopsy yielded malignant cells, and a regimen of aminoglutethimide and hydrocortisone was started. Her condition rapidly worsened and she died on November 15, 1984. An autopsy showed a metastatic poorly differentiated adenocarcinoma originating from the tail of the pancreas and there was no evidence of pituitary adenoma.

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropic hormone
CRF = corticotropin-releasing factor
CT = computed tomography

### Discussion

The pharmacologic studies used for the differential diagnosis between Cushing's disease and ectopic ACTH secretion are based on the fact that pituitary tumor cells are under a certain degree of control from the hypothalamic-pituitary-adrenal axis while ectopic ACTH-producing cells lack such control. Thus, while patients with Cushing's disease tend to have suppressibility of ACTH secretion by high doses of dexamethasone and responsiveness to inhibition of 11-hydroxylase by metyrapone, in patients with ectopic ACTH secretion,

TABLE 1.—*Sensitivity and Specificity of Pharmacologic Tests Used in the Differential Diagnosis of Cushing's Disease Versus Ectopic ACTH Syndrome*

| Pharmacologic Tests | Response | Patients, Percent | Patients, Number | 95% Confidence Limits, Percent |
|---|---|---|---|---|
| *High-Dose Dexamethasone** | | | | |
| Cushing's disease | Suppression | 90 | . . . | . . . |
| | No suppression | 10 | . . . | . . . |
| Ectopic ACTH syndrome . . . . | Suppression | 20 | 12 | 10-30 |
| | No suppression | 80 | 48 | 70-90 |
| *Metyrapone Test** | | | | |
| Cushing's disease | Response | 87 | 150 | 82-92 |
| | No response | 13 | 23 | 8-18 |
| Ectopic ACTH syndrome . . . . | Response | 48 | 16 | 31-65 |
| | No response | 52 | 17 | 34-68 |
| *CRF Test†* | | | | |
| Cushing's disease | Response | 94 | 46 | 68-100 |
| | No response | 6 | 3 | 0-32 |
| Ectopic ACTH syndrome . . . . | Response | 7 | 1 | 0-20 |
| | No response | 93 | 13 | 80-100 |

ACTH=adrenocorticotropic hormone, CRF=corticotropin-releasing factor

*From Findling et al,[6] Sindler et al,[7] Imura et al,[8] Crapo[9] and Howlett et al.[10]
†From Chrousos et at,[11,12] Rohrmoser et al,[13] Orth et al, [14] Müller et al,[15] Nakahara et al,[16] Pieters et al[17] and Lytras et al.[18]

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no suppressibility with dexamethasone and no response to metyrapone are expected. The interpretation of such tests should, however, take into account—in addition to the intra-assay and interassay coefficient of variation for the analytical determinations—that the sensitivity and specificity for Cushing's disease of both these tests are less than 100%. As shown in Table 1, among patients with the ectopic ACTH syndrome, 48% show an apparent response to metyrapone and 20% to dexamethasone.

To achieve a better separation of pituitary versus ectopic sources of ACTH, some authors advocate the use of higher doses of dexamethasone (32 mg) in patients who fail to respond to the standard 8-mg test.[1-3] We warn about using such a maneuver, which is based on a single case report,[4] has not been systematically evaluated and may, as in the case of our patient, lead to an erroneous diagnosis. The availability of CRF, the hypothalamic polypeptide that modulates pituitary ACTH secretion, provides a novel tool for the differential diagnosis of Cushing's syndrome.[5] Review (Table 1) of the 49 published cases of Cushing's disease tested with CRF shows that 46 (94%) patients showed a response while only 3 (6%) patients showed no response and, of the 14 patients with ectopic ACTH secretion, 13 showed no response to CRF and 1 patient showed some responsiveness that was, however, not reproducible. If further data confirm this trend, the CRF test could become very useful in the etiologic diagnosis of Cushing's syndrome and would have a greater sensitivity and specificity than the standard 8-mg dexamethasone test. The addition of this simple test to the diagnostic evaluation could in some patients reduce the need for more invasive and expensive diagnostic procedures such as inferior petrosal sinus catheterization.

#### REFERENCES


1. West CD, Meikle AW: Laboratory tests for the diagnosis of Cushing's syndrome and adrenal insufficiency and factors affecting those tests, chap 94, *In* De Groot LJ, Cahill GF, Odell WD, et al (Eds): Endocrinology, Vol 2. New York, Grune & Stratton, 1979, pp 1171-1172

2. Tyrrell JB, Forsham PH: Glucocorticoids and adrenal androgens, chap 9, *In* Greenspan FS, Forsham PH (Eds): Basic & Clinical Endocrinology, 4th Ed. Los Altos, Lange Medical Publications, 1983, pp 258-294

3. Wand GS, Ney RL: Disorders of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 1985; 14:33-53

4. Linn JE, Bowdoin B, Farmer A, et al: Observations and comments on failure of dexamethasone suppression. N Engl J Med 1967; 277:403-405

5. Chrousos GP, Schuermeyer TH, Doppman J, et al: Clinical applications of corticotropin-releasing factor. Ann Intern Med 1985; 102:344-358

6. Findling JW, Aron DC, Tyrrell JB, et al: Selective venous sampling for ACTH in Cushing's syndrome: Differentiation between Cushing disease and the ectopic ACTH syndrome. Ann Intern Med 1981; 94:647-652

7. Sindler BH, Griffing GT, Melby JC: The superiority of the metyrapone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. Am J Med 1983; 74:657-662

8. Imura H, Matsukura S, Yamamoto H, et al: Studies on ectopic ACTH-producing tumors. Cancer 1975; 35:1430-1437

9. Crapo L: Cushing's syndrome: A review of diagnostic tests. Metabolism 1979; 28:955-977

10. Howlett TA, Rees LH, Besser GM: Cushing's syndrome. Clin Endocrinol Metab 1985; 14:911-945

11. Chrousos GP, Schulte HM, Oldfield EH, et al: The corticotropin-releasing factor stimulation test. N Engl J Med 1984; 310:622-626

12. Chrousos GP, Nieman L, Nisula B, et al: Corticotropin-releasing factor stimulation test. N Engl J Med 1984; 311:472-473

13. Rohrmoser B, Lüdecke DK, Scriba PC: Inconsistent stimulation of plasma ACTH through corticotropin-releasing factor in a patient with central Cushing's disease due to pituitary adenoma. Klin Wochenschr 1985; 63:475-477

14. Orth DN, DeBold CR, DeCherney GS, et al: Pituitary microadenomas causing Cushing's disease respond to corticotropin-releasing factor. J Clin Endocrinol Metab 1982; 55:1017-1019

15. Müller OA, Stalla GK, von Werder K: Corticotropin releasing factor: A new tool for the differential diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 1983; 57:227-229

16. Nakahara M, Shibasaki T, Shizume K, et al: Corticotropin-releasing factor test in normal subjects and patients with hypothalamic-pituitary-adrenal disorders. J Clin Endocrinol Metab 1983; 57:963-968

17. Pieters GFFM, Hermus ARMM, Smals AGH, et al: Responsiveness of the hypophyseal-adrenocortical axis to corticotropin-releasing factor in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 1983; 57:513-516

18. Lytras N, Grossman A, Perry L, et al: Corticotropin releasing factor: Responses in normal subjects and patients with disorders of the hypothalamus and pituitary. Clin Endocrinol (Oxf) 1984; 20:71-84


# Acquired Immunodeficiency Syndrome Presenting as Schizophrenia


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SEVERAL INVESTIGATORS have reported affective and psychotic symptoms with the acquired immunodeficiency syndrome (AIDS). Nurnberg and co-workers reported the case of a 28-year-old man with AIDS who presented with command hallucinations, persecutory delusions, anorexia, a 13.6-kg weight loss (30 lb), anhedonia, abulia, middle insomnia, psychomotor retardation and impaired recent memory.[1] Hoffman reviewed two AIDS cases that had in common a psychiatric presentation and diffuse cerebral atrophy indicated by computed tomography.[2] One case was characterized as progressive dementia and the other as transient acute encephalopathy. Kermani and associates identified a triad of mood disturbance, thought disorder with grandiose delusions and severe memory deficits in a series of three patients with AIDS.[3] Subsequently, Kermani and colleagues described the case of an AIDS patient who presented with manic features before development of cognitive and memory impairment,[4] while Thomas and co-workers reported seeing a 22-year-old patient with AIDS who had a paranoid psychosis but normal cognitive and memory functions.[5]

We report a case further illustrating the protean presentation of psychiatric signs and symptoms in AIDS patients and define one pathway—a natural history culminating in dementia. The case is remarkable because of a prolonged course that began with subtle organicity, was punctuated by psychotic decompensation and progressed to profound dementia.

## Report of a Case

The patient, a 32-year-old single, bisexual man, was brought to the psychiatric emergency service by his sister. She stated that for the past nine months he had increasing apathy, social withdrawal to the point of almost total isolation and bizarre behavior such as urinating in public. The initial


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